PERSPECTIVE

Consequences of hepatic damage after traumatic brain injury: current outlook and potential therapeutic targets

Traumatic brain injury(TBI) triggers liver inflammation: TBI is a serious pathology affecting around 10 million people annually, being a persistent public health and medical problem. Forceful impact while playing sports, falls, physical assault, or traffic accidents are common causes of head injury. Consequences of TBI include: chronic headaches, seizures, erratic behavior, loss of coordination, loss of memory and consciousness, slurred speech, and coma. Although TBI has long term consequences due to the immediate loss of brain tissue, treatment has focused on mitigating secondary damage. Yet there exist more that 30 clinical trials for TBI that fail despite successful experimental data (Maas et al., 2010). Most of these studies were based on neuroprotective treatments to reduce inflammation and neurodegeneration in the injured brain, and improve motor and cognitive outcomes. However, injury to the brain also produces alterations in the bloodstream and peripheral organs. Recent breakthroughs in brain injury research investigate the link between brain inflammation and peripheral organs; and one of the most sensitive organs to inflammation is the liver. The systemic production of cytokines and chemokines by the liver and other organs, in response to the brain damage, is an essential factor of the inflammatory secondary response in the brain due to communication of brain-periphery. Recent studies have demonstrated that focal injury to the brain elicits a rapid hepatic response (Anthony et al., 2012), the production of chemokines by the liver acts as an amplifier of the focal injury response providing a route of CNS-liver communication. These molecular signals of communication, initiated by the injured brain, are transmitted to the periphery that plays an important role in the regulation of the CNS inflammatory response (**Figure 1A**). Yet, how these mediators of inflammatory response contribute to the detrimental sequelae of TBI remains unknown. In summary, while the bidirectional pathways between the brain and the peripheral system are important in the pathogenesis of CNS injuries, they are not well understood.

Systemic acute phase response induced after traumatic brain injury: After suffering brain damage, rapid microglial activation and the release of pro-inflammatory cytokines occur in the pericontusional regions surrounding the site of the impact (necrotic brain tissue). Other inflammatory cells, such as neutrophils and macrophages, are the source of toxic metabolites, able to release a matrix of metalloproteinases that lead to the formation of axonal bulbs and neuronal damage. The activation of these inflammatory cells is not restricted to the CNS parenchyma; greater increase in neutrophils and leukocyte recruitment occurs in the peripheral system. Yet these signals might not be released from the CNS after injury; they are commonly released from damaged peripheral organs to activate leukocyte mobilization and priming. If the stimulus is sufficiently strong, this elevated level of circulating leukocytes is accompanied by fever and changes in the serum levels. Furthermore, inflammatory cells from the circulation are accumulated in organs, such as the liver, lung, heart or kidney, leading to organ inflammation. The aforementioned changes are commonly referred to as the systemic acute phase response (APR), and the liver is the principal organ involved in inducing and coordinating this response. The liver contains the highest number of resident macrophages of any other organ, and is the major contributor to the level of chemokines in serum after brain injury. Therefore, TBI has been shown to be directly associated with a systemic APR. After acute brain injury, the chemokine expression by the liver results in neutrophil recruitment and hepatic damage, contributing to multi-organ dysfunction. Furthermore, it is widely accepted that the pro-inflammatory cytokines IL-1β, IL-6, and TNFα, or chemokines such as CCL1, CCL2 or CCL10, are critical mediators of APR after brain injury (Woodcock and Morganti-Kossmann, 2013). Systemic inhibition studies show that cytokine and chemokine induction in the liver regulates the focal inflammatory response in the brain. Hepatic chemokine release amplifies the local injury response by increasing the circulating immune cells in the blood to migrate into the injured brain. Yet leukocyte recruitment to the brain also may be dependent on hepatic chemokine and APR production, making their inhibition a useful therapeutic target.

Role of serum amyloid A protein as an inflammatory mediator after brain injury: Serum amyloid A (SAA) is an acute-phase protein with pleiotropic cytokine-like properties as part

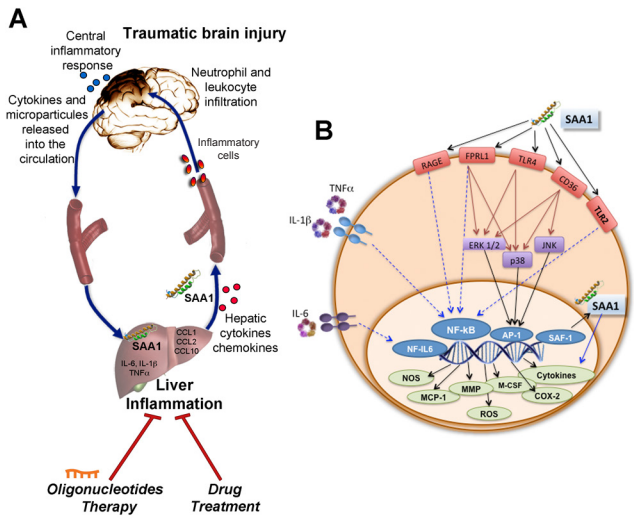

Figure 1 Brain-liver communication.
(A) The interplay between the brain and liver after traumatic brain injury (TBI). TBI induces central and peripheral inflammation and triggers the induction of acute phase response. Serum amyloid A1 (SAA1) is produced and secreted by the damaged liver. The inhibition of SAA1 using pharmacological or oligonucleotides therapies could abolish neurotoxicity in the brain. (B) SAA1 receptors and signaling pathways. SAA1 can bind the receptors RAGE (receptor for advanced glycation end-products), FPRL1 (formyl peptide receptor-like 1), CD36 (cluster of differentiation 36), or TLR2/4 (Toll-like receptors 2 or 4). SAA1 induces the activation of ERK (extracellular signal-regulated kinase) and JNK (c-Jun N-terminal kinase)/p38 signaling pathways activating the transcription factors NF-kB (nuclear factor kappa B), AP-1 (activating protein 1) or the SAA-activating factor 1 (SAF-1) that induces the production of SAA1. Consequently, SAA1 stimulates the expression of MCP-1 (monocyte chemoattractant protein 1), MMP (matrix metalloproteinase), NOS (nitric oxide synthetase), M-CSF (macrophage colony-stimulating factor), ROS (reactive oxygen species), COX-2 (cyclooxygenase-2) or pro-inflammatory cytokines. Alternatively, SAA1 synthesis can be induced by TNFα (tumor necrosis factor-alpha), IL-1β or IL-6.

of the APR (Jensen and Whitehead, 1998). Circulating SAA increases up to 1,000-fold in response to systemic inflammation. In mice, two of the four functional isoforms of SAA, isoform 1 and 2 expression and synthesis in the liver, are induced in response to pro-inflammatory stimuli. The main inducers of SAA1 production are IL-1β, IL-6 and TNFα, which bind to their designated receptors in many cell types (**Figure 1B**). The involvement of SAA has been established in several pathologies. Therefore, SAA1 is a powerful pro-inflammatory mediator as it can both bind to several receptors expressed in various cell types (including epithelial cells, fibroblasts, lymphocytes, endothelial cells, monocytes/macrophages, smooth muscle cells and adipocytes) and induce the activation of several signaling pathways. Also, SAA1 binds to neutrophils, inducing a microenvironment that promotes the expansion of regulatory T cells at sites of infection or injury. SAA1 acts as the physiological pro-inflammatory mediator that is able to induce the gene expression of IL-1A, IL-1B, IL-8, IL-6 and TNFα in human macrophages that differentiate from peripheral monocytes, both of which peak at early hours after TBI. The release of IL-1β by SAA1 is dependent on caspase-1 activity, suggesting the activation of the inflammasome cascade. In addition, SAA1 induces changes in the morphology, proliferation, survival, ROS production and iNOS expression in murine microglia and astrocytes, through glial receptors TLR2, TLR4 and FPR2 and the activation of PI3K signaling pathway (Yu et al., 2014) (**Figure 1B**).

Treatments of SAA-induced central and peripheral inflammation: Although the brain exists in the body and is intimately connected to the periphery, research in TBI has largely ignored this fact and has focused on CNS-specific biomarkers of brain injury. Thus, SAA1 also present in the bloodstream during initial hours after TBI might be a relevant biomarker to indicate the severity of damage. Human studies have shown SAA1 concentrations in plasma at day 1 after hypoxic-ischemic encephalopathy (HIE) to be correlated with the severity of damage in neonates (Aly et al., 2011), as well as in TBI adult patients (Gao et al., 2014). Additionally, we have demonstrated that hepatic and circulating SAA1 expression increases a few hours after TBI and then is reduced by a powerful anti-inflammatory angiotensin receptor blocker (Villapol et al., 2015). We also have observed an increase in chemokines expression CCL1 and CCL10, macrophages and dying cells in the liver, demonstrating hepatic inflammation after TBI (Villapol et al., 2015).

The interplay between the peripheral immune system and the APR with respect to the outcome of brain injury remains poorly understood. Since SAA1 induces inflammatory mediators and recruitment of inflammatory cells, hepatic SAA1 may represent a useful therapeutic target after acute brain injury. Several approaches can be taken to reduce the inflammatory activity of SAA1. The inhibition of SAA1 production may also protect against the systemic sequelae of acute TBI. There exist pharmacological agents, such as colchicine, that reduce the hepatic production of SAA1 and that was used as treatment for the amyloidosis pathology (Meneses et al., 2015). Additionally, antisense therapy using oligonucleotides specific to target the splicing and synthesis of SAA1 (Kluve-Beckerman et al., 2011) may be useful tools to block the SAA1 production stimulated after brain injury. In summary, inhibition of the harmful effects of SAA1, or reducing its serum levels, would have an impact not only on hepatic inflammation, but also on secondary inflammatory response after TBI. However, another alternative avenue for TBI therapy could be to seek pharmacological inhibitor of specific receptors of inflammatory cells that migrate from the periphery.

Conclusions: The blockade of inflammatory intermediaries of the liver after brain injury could effectively alter the recruitment of leukocytes to the brain, an important factor to consider when peripheral inflammation exacerbates the progression of brain damage. As an acute phase protein with pleiotropic pro-inflammatory properties, SAA1 may represent an important link between brain injury and hepatic and systemic inflammation. Yet, there is also evidence to suggest that systemic inflammation confers a degree of tolerance to brain injury. Like the liver, other secondary organs damaged by similar pathologies observed in patients with acute brain injury may also represent alternative therapeutic targets for improving clinical outcome. In conclusion, since inflammation appears to be a common link between brain injury and the periphery, one is led to hypothesize that inflammatory signals released after TBI could regulate components of hepatic response and that consequently exacerbate inflammatory response in the brain.

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